

## **Roche Position<sup>1</sup> on Similar Biotherapeutic Products – Biosimilars**

### **Similar Biotherapeutic Products – Biosimilars**

Innovative biotherapeutic products (e.g. monoclonal antibodies) are losing market exclusivity, and products claimed to be similar to an innovative product are being developed and commercialised.

While it is relatively easy to copy small molecule products produced by chemical synthesis, it is very challenging to copy biotherapeutic products as they have complex molecular structures and are obtained in living systems through highly complex manufacturing processes, which are difficult to reproduce identically. At this time analytical, pre-clinical or clinical tests alone are unable to fully characterise a biotherapeutic product. As such, in order to establish if a product is similar to an innovator in terms of molecular properties, safety and efficacy, it is critical to ensure that a comprehensive data package is available comprising all three levels of analysis.

“Similar” biotherapeutic products are similar, but not identical, to the innovator product and therefore the term “biogeneric” is inappropriate. In addition, the testing required to develop “similar” biotherapeutic products is more demanding than that of traditional generics due to the aforementioned complexity of molecular structures and the challenging nature of their production. As such, based on globally shared scientific understanding as set forth by organisations such as the World Health Organization (WHO) in its guidance on similar biotherapeutic products (see below), these products are also referred to as “biosimilars”, “similar biotherapeutic products”, “subsequent entry biologics” or “follow-on protein products”.

We are committed to meeting high ethical standards in all our undertakings and to maintaining the trust of both the doctors who prescribe and the patients who rely on the quality, safety and efficacy of our products. While we respect the legitimate undertakings of our competitors, including biosimilar manufacturers, we expect that our competitors comply with applicable laws and regulations.

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<sup>1</sup> Pertains to SDGs 3 and 16

## **The need for a well-defined regulatory framework for biosimilars**

Due to the complex nature of these diverse products for which similarity to one reference product has to be demonstrated and the benefit/risk profile carefully monitored, a well-defined and transparent regulatory framework covering development, approval and post-authorisation procedures must be in place.

In 2005, the first regulatory framework for biosimilars was established by regulatory authorities in the European Union (EU) and several biosimilars have since been approved based on these guidelines. Additionally, the principles laid down in European Medicines Agency (EMA) guidelines on biosimilar medicinal products have been adopted by the expert committee on biological standardisation of the WHO in its guidelines (Evaluation of similar biotherapeutic products [SBPs]). In the United States, the Food & Drug Administration (FDA) issued draft guidance documents following legislation demanding a specific regulatory pathway for biosimilars. These draft guidance documents will be completed by future provisions, e.g. on interchangeability. In many other countries, guidelines for the approval of biosimilars have either already been adopted or are under discussion.

We support the development of regulatory frameworks for the introduction of biosimilars and are actively engaged in stakeholder dialogue. Such frameworks help to ensure that there is a high and consistent level of public health protection that applies to biosimilars, on the same basis as it applies to innovator/originator products. In addition, it is our strong belief that regulations relating to biosimilars should not impede, but rather promote and give incentive for, innovative research towards the development of new medicines. Accordingly, it contributes to our commitment to support the United Nations (UN) Sustainability Development Goals (SDGs), in particular SDG 3 on health, within the sphere of our business strategy.

Marketed biotherapeutic products range in molecular complexity from relatively small, unglycosylated proteins (such as insulin or somatropin), to very large and complex glycoproteins that may possess multiple functions mediated by different parts of the molecule (e.g. monoclonal antibodies) or are involved in several biological pathways (e.g. interferons). Due to these different requirements, the scope of the clinical evidence required to support the approval of biosimilar medicinal products should be defined on a case-by-case basis.

The approval of biosimilars via a specific regulatory pathway can only be justified when based on the principle of similarity, i.e. comparison with a defined reference product for which extensive experience is available. The demonstration of similarity has to include

head-to-head, quality-related, non-clinical, as well as clinical studies conducted in appropriately sensitive populations.

If a biotherapeutic product intended to be a copy of a reference product is approved but does not meet WHO criteria for biosimilars, i.e. has not been demonstrated to be similar with regard to quality or non-clinical properties as well as clinical safety and efficacy in head-to-head comparative studies, it should not be called a biosimilar. Rather it should be called a non-comparable biologic (NCB). Unless a manufacturer provides all necessary scientific evidence qualifying its product as a biosimilar, any approval of a NCB should be reassessed by the National Health Agency because of the potentially significant differences in regard of quality, safety and efficacy between the NCB and the reference biotherapeutic product. Manufacturers who bring a biotherapeutic product to the market and claim their product is a “biosimilar” without meeting the WHO criteria for biosimilars are not acting in a transparent and responsible manner. We will continue to take all necessary steps to avoid related misunderstandings and will oppose the use of misleading claims that are unsubstantiated due to lack of reasonable data.

### **Comparability and Similarity – similar concepts but different knowledge base**

Demonstrating that a proposed protein product is biosimilar to a reference product produced by a different manufacturer will require more extensive and comprehensive data than that required to assess the comparability of a product before and after an incremental manufacturing process change made by the innovator.

A manufacturer who modifies an established and approved manufacturing process will have extensive knowledge and information about the product and the existing process, including established controls, acceptance parameters and a broad analytical data base that is linked to the products’ clinical development experience. This will facilitate the establishment of analytical comparability, e.g. the demonstration that pre- and post-change products are highly similar with respect to safety and efficacy. In contrast, the manufacturer of a proposed biosimilar product will likely have a different manufacturing process (e.g. different cell line, raw materials, equipment, processes, process controls, and acceptance criteria) from that of the reference product and no direct knowledge of the manufacturing process for the reference product. Given the structural complexity of biotherapeutic products, differences between the proposed biosimilar product and the reference product are expected. In the absence of clinical development experience, the potential impact of these differences on safety and efficacy cannot be predicted from analytical assessment alone.

As such, the data requirements for biosimilars will be higher and should always include comparative pre-clinical and clinical studies obtained prior to the marketing authorisation.

## **Patient safety as a crucial element when considering biosimilars**

### ***The need for appropriate data***

Despite the fact that biosimilar and reference drugs can show similar efficacy, the biosimilar may exhibit a different safety profile in terms of the nature, seriousness or incidence of adverse reactions. Data from pre-authorisation clinical studies are normally insufficient to identify all potential differences. Safety signals seen with biotherapeutic products can often be related to their mechanism of action and/or their high degree of target specificity. In addition, all biotherapeutic products have the potential to cause immunogenic events that may sometimes take years to develop, may only occur infrequently, could likely be different in different indications and may have profound clinical consequences. This cannot be predicted using analytical assays or preclinical models, and therefore must always be evaluated in a clinical setting.

Regulatory authorities and experts agree that both non-clinical and clinical data, including an assessment of the risk of immunogenicity, are needed in order to demonstrate similar safety and efficacy profiles of a biosimilar compared to the reference product. This risk must be assessed pre-approval in comparative clinical studies of appropriate size and duration. These studies must include homogeneous and sensitive patient populations. Additionally, as with all new products, post-authorisation pharmacovigilance and relevant epidemiology data must be an essential part of a risk management programme, requiring clear identification of the product used.

We believe that any extrapolation of clinical efficacy, safety or immunogenicity data to additional indications of the reference product requires sound scientific justification including the fact that the respective clinical similarity assessment has been done in the most sensitive patient populations and thus the risk of any clinically relevant differences is appropriately mitigated.

### ***The need for an individualised label***

Labelling of biosimilars should be individualised and should clearly indicate which clinical safety and efficacy data have been obtained with the biosimilars. It should also identify any differences in the safety profile. The labels of all biotherapeutic products, including biosimilars, should be worded in a way that allows physicians to make a conscious treatment

decision and to comply with their duty to inform patients about product-specific characteristics and risks, also in comparison to other products.

### ***The need for unique identification of biotherapeutic products***

It is essential to be able to identify and trace every biological medicinal product used, in case any adverse reactions should occur. Therefore, biosimilars must be branded in a way to enable authorities to unequivocally identify the specific biological product used in clinical practice. For safe prescription, dispensing and effective pharmacovigilance monitoring it is necessary that different products (including biosimilars) can be identified and traced by unique identifier(s) [e.g. using a biologic qualifier that follows the INNs]. Automatic substitution without the consent of the prescribing physician should therefore not be an acceptable practice. In order to improve the traceability of biotherapeutic products, the trade name of the administered product should also be clearly recorded (or stated) in the patient file.

Switching patients back and forth between different biopharmaceuticals may pose additional risk. This necessitates the understanding that the marketing and utilisation of biosimilars does not imply that automatic substitution with a reference product, and/or interchangeability without the consent of a qualified healthcare professional is an acceptable practice.

### **Support physician's ability to prescribe based on criteria beyond price**

We support the physician's ability to prescribe based on their assessment of the totality of data available, their personal experience, and in their patient's best interest. Hence, tender or reimbursement policy decisions should not unduly limit treatment options. Such decisions should not force patients already on treatment to be switched for non-medical reasons, or to be treated off-label. Considerations should go beyond price and include other relevant factors such as the totality of data available, delivery of value, formulation and services, taking into account individual patient characteristics, patient / caregiver values, and respecting clinical judgment.

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